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SYNTHESIS OF N-ALKYL-N-HYDROXYAMPHETAMINES AND RELATED NITRONES

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Abstract—The action of *m*-chloroperbenzoic acid on various amphetamines and on dibenzylamine is shown to yield N-hydroxy derivatives and related nitrones.

Authentic samples of some N-alkyl-N-hydroxy-2-amino-1-phenylpropanes were required to help identify metabolites of various amphetamines and permit their quantitative determination. A simple preparative method of oxidising the amphetamine to its N-hydroxy derivative was envisaged since N-alkyl-amphetamines are commercially available or are readily prepared from amphetamine.

There are few references to reactions which produce N-hydroxyamines from the corresponding amines. Hydrogen peroxide has been used as an oxidising agent[1,2] but this reagent proved unsatisfactory in the present study. Mixtures of products were obtained when N-ethyl-2-amino-1-phenylpropane (ethylamphetamine) was oxidised with H_2O_2; a significant amount of dealkylation to amphetamine was observed by means of GLC.

A number of secondary amines have been oxidised to N-hydroxyamines by the reaction of the amine with benzoyl peroxide followed by hydrolysis of the resulting ester with NaOEt.[3] The preparation of N,N-dibenzylhydroxylamine (2) from dibenzylamine is typical (Fig 1). An attempt was made to prepare N-hydroxy-N-methylamphetamine by reacting equimolecular quantities of N-methylamphetamine and benzoylperoxide in dry diethyl ether. An oil was obtained which gave an IR spectrum consistent with the ester $PhCH_2CHMeN(OCOPh)Me$ (ν_{max} 1721 cm^{-1}). This ester was not hydrolysed by cold NaOEt and when hydrolysis was attempted at reflux temperature, the major products [identified by GLC retention times (T_R)] were 1-phenyl-2-propanone and its oxime. Milder hydrolysis with NH_4OH for 24 hr resulted in only partial hydrolysis and produced mixtures (GLC evidence).

More recently, Craig and Purushothaman[4] showed that the N-oxides of some tertiary amines may be prepared in excellent yields 5 using *m*-chloroperbenzoic acid (CPBA) as the oxidising agent and that the reaction proceeded *via* the N-(*m*-chlorobenzoyloxy) ester. This reagent has not previously been used for the oxidation of aliphatic secondary amines; however, it appeared probable that N-(*m*-chlorobenzoyloxy) derivatives may be obtained in this way. Since it had been established that hydrolysis of such derivatives to N-hydroxy amphetamines was not practical, an alternative method of producing N-hydroxy derivatives from N-(*m*-chlorobenzoyloxy) derivatives was required. Reduction by means of LAH seemed feasible, so the known O-benzoyl-N,N-dibenzylhydroxylamine (1) was prepared and reduced by LAH to N,N-dibenzylhydroxylamine (2) in excellent yield. A number of N-aroyloxyamphetamines were synthesised and their conversion to N-hydroxyamphetamines investigated. The oxidant selected was CPBA since, due to its solubility in K_2CO_3 solution, excess reagent could be readily removed from the mixture.

When N-benzylamphetamine (3) reacted with two equiv of CPBA, a solid product was obtained and partitioned between K_2CO_3 solution and ether. The ether-soluble material was a mixture of a solid ($C_{16}H_{17}NO$; compound A) and an oil (ν_{max} 1721 cm^{-1}). Reduction of the latter with LAH gave another oil, the IR of which lacked CO absorption. This product was basic and formed an acid oxalate ($C_{18}H_{21}NO_5$) which was identified as N-benzyl-N-hydroxyamphetamine (4) oxalate. It rapidly reduced yellow mercuric oxide and in so doing was

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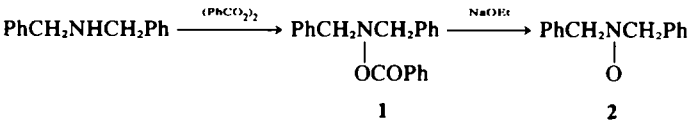

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Fig 1.

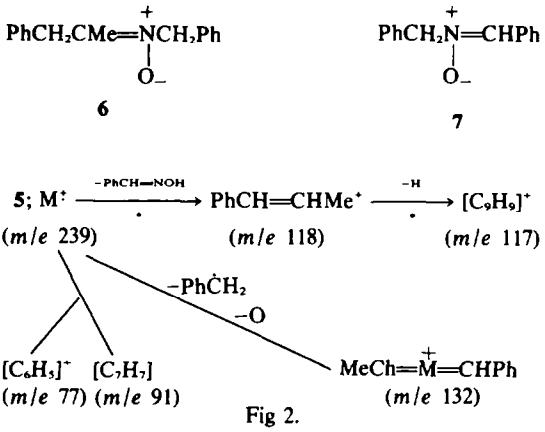


Fig 2.

converted to compound A. The latter was readily reduced by LAH back to **4**.

This behaviour is consistent with compound A being a nitrone[5,6] of structure **5** or **6**. Its UV (λ_{max} 298·5 nm) and mass spectrum supported structure **5** in which the nitrone double bond was in conjugation with the phenyl ring. The MS showed a molecular ion (*m/e* 239) of low abundance and only five major fragment ions (relative abundance 10% or greater) which are identified in Fig 2. An examination of its NMR spectrum confirmed that compound A was N-(1-benzylethyl)-α-phenylnitrone (**5**). The Me signal was a doublet (δ 1·55, J = 6·5) and the N=CH proton a singlet (δ 7·04). The action of CPBA on N-benzylamphetamine, therefore, can be summarized (Fig 3).

Further confirmation that excess CPBA reacts with secondary amines to produce nitrones was obtained when dibenzylamine was converted to N-benzyl-α-phenylnitrone (**7**) by this reagent. Subsequent LAH reduction of this nitrone gave an excellent yield of N,N-dibenzylhydroxylamine (**2**).

Other N-alkyl-N-hydroxyamphetamines (**9a–9h**) were conveniently prepared in by treating the appropriate N-alkylamphetamine (**8**) with 2·2 equiv of CPBA, then reducing the products with LAH. Complete conversion of the amphetamine to its N-hydroxy derivative did not occur. A GLC examination of the ether-soluble products obtained after the reduction revealed that, in addition to the required N-alkyl-N-hydroxyamphetamine, the solution contained starting material, some oxime (**10**) and additional minor products. Unreacted starting material (**8**) was removed from the ether solution by extracting the latter with an aqueous buffer of appropriate pH value (Table 1). The N-hydroxyamphetamine was then precipitated from the ether solution as its oxalate. In some instances, basic components in the ether extract were first precipitated as a mixture of oxalates prior to being partitioned between ether and aqueous buffer.

The eight N-alkyl-N-hydroxyamphetamines (**9a–9h**) obtained by this method were characterized by the following reactions. Each gave a black spot when thin layer chromatograms were sprayed with Tollen's reagent; hydroxylamines are known[7,8] to reduce ammoniacal silver nitrate solution.

When each compound was shaken with yellow mercuric oxide,[9] the oxide was reduced to mercury while the N-hydroxy compound was simultaneously oxidised, in most instances to a nitrone as a major product. The N-methyl compound (**9a**) behaved atypically; GLC evidence indicated that it was converted to the oxime (**10**, R′ = H) and an unidentified product. In addition, when diethyl ether solutions of the nitrones obtained were subsequently reduced with LAH, the N-hydroxy compounds were regenerated.

With one exception (**9h**) each N-hydroxyamphetamine gave a single peak when examined by GLC and when this peak was scanned in a mass spectrometer, the diagnostic ion, $CH_3CH{=}\dot{N}(OH)CH_2R^2$, was an abundant fragment. This ion is related to the $CH_3CH{=}\dot{N}HCH_2R^2$ ion which was the base peak in the MS of the parent amines (**8**). All the hydroxylamines **9** were readily reduced by $TiCl_3$ to the corresponding amine but were unaffected by LAH. Each hydroxylamine was

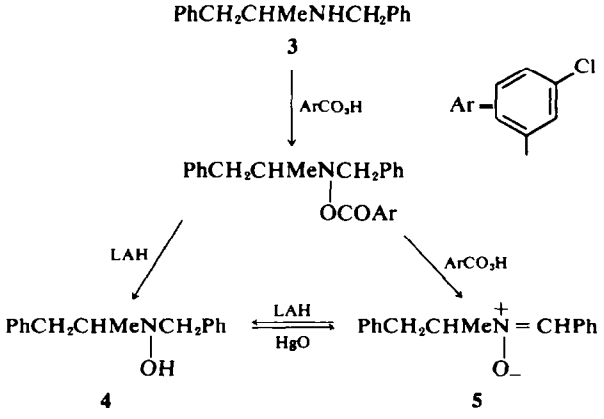
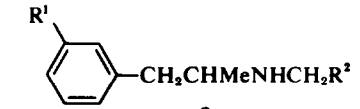


Fig 3.

Table 1. N-Alkyl-N-hydroxyamphetamine oxalates

Compound	Buffer pH	m.p.°C	Formula*	Analysis Found C	Found H	Found N	Calc. C	Calc. H	Calc. N
9a	5·5	148–149	$C_{12}H_{17}NO_5$	55·98	6·71	5·51	56·47	6·61	5·49
b	4·0	161–162	$C_{24}H_{36}N_2O_6$	63·64	8·02	6·18	64·26	8·09	6·25
c	4·6	136–139	$C_{26}H_{40}N_2O_6 . H_2O$	63·46	8·20	5·46	63·13	8·56	5·66
d	4·0	157–159	$C_{15}H_{23}NO_5$	60·52	7·86	4·90	60·59	7·80	4·71
e	3·0	152–153	$C_{14}H_{18}F_3NO_5$	49·82	5·46	4·25	49·85	5·38	4·15
f	3·0	142–143	$C_{28}H_{36}F_6N_2O_6$	54·91	6·29	4·62	54·90	6·25	4·57
g	3·0	134–135	$C_{30}H_{42}F_6N_2O_6$	56·39	6·44	4·57	56·24	6·61	4·39
h	3·0	129–130	$C_{14}H_{18}F_3NO$	47·76	5·13	4·13	47·59	5·14	3·96

*Compounds with one N atom are acid oxalates.



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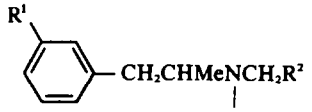

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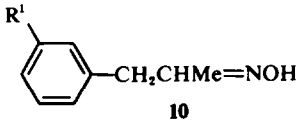

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	R^1	R^2		R^1	R^2
a	H	H	**e**	CF_3	Me
b	H	Me	**f**	CF_3	Et
c	H	Et	**g**	CF_3	nPr
d	H	nPr	**h**	CF_3	CH_2OH

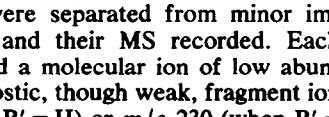
converted to the oxime (**10**) when shaken with NaOH/air (GLC evidence). N-hydroxyamphetamine is known[10] to undergo a similar conversion to benzymethylketoxime. Hydroxylamine **9h** is an *in vitro* metabolite of N-2-hydroxyethyl*nor*fenfluramine.[11] It is considerably less stable than the other hydroxylamines (**9**) on GLC, and during GLC/MS treatment it undergoes complete decomposition, mainly to the amine.

The nitrones formed in the mercuric oxide reaction were isolated as oils in quantities insufficient for purification and complete characterisation. Their facile reduction back to N-alkyl-N-hydroxyamphetamines by LAH confirmed that they were nitrones and not the isomeric oxaziranes[6,12] and indicated they possessed one of two structures (**11** or **12**), comparable to structure **5** and **6**. The nitrones were separated from minor impurities by GLC and their MS recorded. Each spectrum displayed a molecular ion of low abundance and a diagnostic, though weak, fragment ion of *m/e* 162 (when R′ = H) or *m/e* 230 (when R′ = CF_3), which obviously was formed by explusion of an R^2 radical from the N-alkyl side chain. A complete interpretation of the MS, however, did not permit a choice between the two possible structures. Attempts are being made to prepare pure N-alkylnitrones in quantities sufficient for an NMR study to resolve this question.

The eight N-alkylamphetamines (**8a–8h**) and N-benzylamphetamine (**3**) were metabolised *in vitro* with a homogenised guinea pig liver preparation (10,000 g supernatant). In all instances, N-hydroxy metabolites (**9** and **4**) were isolated[13] and these metabolites were identical in TLC, GLC and MS behaviour with the synthetic products described. In addition, each N-hydroxy metabolite was converted to a nitrone by treatment with yellow mercuric oxide. These products also showed TLC, GLC and MS behaviour identical with that of the nitrones prepared from synthetic N-hydroxyamphetamines.

EXPERIMENTAL

M.ps (capillary tubes) are uncorrected, IR spectra were recorded on a Unicam SP1000 spectrophotometer as



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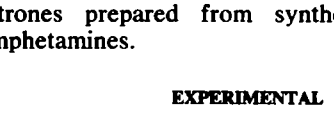

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Nujol mulls and NMR spectra were taken on a 60 MHz Perkin-Elmer R-10 spectrophotometer with TMS as internal standard. Direct inlet MS were recorded on an A.E.I. MS-9 or MS-12 mass spectrometer at an ionization potential of 70 eV and source temperature of 180–200°. GLC was performed on a Perkin-Elmer F-11 instrument which incorporated a flame-ionization detector. Two columns were used (a) a glass column, length 1 metre, o.d. 0·25 in containing 7½% Carbowax on Chromosorb W, 100–120 mesh, acid-washed and DCMS-treated, (b) a glass column, length 2 metres, o.d. 0·25 in containing 2% OV-17 on Chromosorb G 80–100 mesh, acid-washed and DMCS-treated. N_2 was the carrier gas.

Combined GLC/MS were recorded on a Perkin-Elmer 200 instrument on a column identical to column (a) described above. Helium (10 lbs/sq in) was employed as the carrier gas and an ionizing potential of 70 eV was again employed. The relevant temps were as follows: oven 160–180°, injection port 180–200°, manifold 215°, ion source 185°.

Action of m-*chloroperbenzoic acid on* N-*benzylamphetamine.* To a cooled (0–5°) soln of N-benzylamphetamine (2·25g) in dry acetone (25 ml) was added dropwise a soln of *m*-chloroperbenzoic acid (3·5 g) in dry acetone (20 ml). After addition was complete (15 min), the resulting soln was left for 30 min at 4° then for 2 hr at room temp. The solvent was removed *in vacuo* and gave a colourless solid which was dissolved in ether (50 ml) and extracted with 10% K_2CO_3 (2 × 20 ml) and water (10 ml). The aqueous extracts were discarded. Evaporation of the dried (Na_2SO_4) ether soln gave a pale yellow oil which solidified on standing. This was triturated with cold ether and filtered to give a colourless solid (compound A; 0·94g), m.p. 87–88·5° (from ether/light petroleum 40–60°). Evaporation of the filtrate gave a pale yellow oil (1·25 g) which was treated as described below.

Compound A was identified as **5**, UV λ_{max} (n-heptane): 298·5 nm, log ϵ = 4·213. Lit[14] λ_{max} for related nitrone (**7**): 300 nm, MS: *m/e* 239 (2% rel.abund.) ($C_{16}H_{17}NO$); NMR ($CDCl_3$) δ 1·55 (d, 3H, J = 6·5, CH_3); 2·60–3·70 (m, 2H, CH_2); 4·15 (m, 1H, $CHCH_3$); 7·04 (s, 1H, CH=N); 8·00–8·25 (m, 2H, *ortho*-protons on α-phenyl); 7·15–7·50 (m, 8H, remaining aromatic protons). Found: C, 80·05; H, 7·20; N, 5·94. Calc. for $C_{16}H_{17}NO$: C, 80·33; H, 7·11; N, 5·86%.

The yellow oil (1·25 g) described above, IR ν_{max} 1721 (C=O) cm^{-1}, was dissolved in dry ether (30 ml) and added dropwise over a 30 min period to a cooled suspension of LAH (0·25 g) in dry ether (20 ml). Subsequent treatment was identical to that described in the preparation of **2**. On evaporating the combined ether extract, a pale yellow oil (1·01 g) was obtained; IR, broad OH absorption (2500–3400 cm^{-1}), C=O absent. The oil was redissolved in dry ether (20 ml) and an excess of a sat soln of $(COOH)_2$ in dry ether was added, with pptn of **4** acid oxalate (0·87 g), m.p. 174–176° (from EtOH). This compound rapidly reduced Tollen's reagent. NMR (DMSO-d_6) δ 1·04 (d, 3H, J = 7, CH_3); 2·60–3·60 (m, 2H, CH_2CH); 2·91 (s, 2H, CH_2N); 7·20 (s, 5H) and 7·28 (s, 5H) (aromatic protons); 8·50 (broad s, 3H, exchanges with D_2O, NHOH and COOH); CH multiplet indistinguishable from background. Found: C, 64·98; H, 6·30; N, 4·30. Calc. for $C_{18}H_{21}NO_5$: C, 65·26; H, 6·34; N, 4·23%.

Interconversion of compounds **4** *and* **5**. This conversion was monitored by GLC. Retention times (T_R) on the 7½% Carbowax column (oven temp 197°; carrier gas 40 lbs/sq in) of **4** and the **5** were predetermined as 12·2 and 22·3 min respectively.

A soln of **5** (0·20 g) in dry ether (50 ml) was reduced with LAH (0·1 g) in dry ether (10 ml) as described for the preparation of **2**, method (a). When a portion (5 μl) of the final ether soln containing the reduced product was spotted on filter paper and sprayed with Tollen's reagent, an immediate black colour developed. When another portion (2 μl) was examined by GLC under the conditions described, the major peak (89%) had T_R 12·2 min. The nitrone peak (T_R 22·3 min) was virtually absent (5%). The ether soln was treated with excess $(COOH)_2$ in dry ether and **4** acid oxalate (0·249 g), m.p. 174–176° precipitated.

N-Benzyl-N-hydroxyamphetamine base was liberated from the oxalate (100 mg) and dissolved in acetone (5 ml) containing water (0·5 ml). To this soln, yellow HgO (50 mg) was added and the mixture shaken. A grey colour developed almost immediately. After 15 min the mixture was filtered, diluted with water (10 ml) and extracted with ether (25 ml). The colourless ether soln no longer caused rapid reduction of Tollen's reagent. GLC of a portion (2 μl) of the ether soln gave one major peak, T_R 22·3 min, indicative of nitrone formation.

O-*Benzoyl*-N,N-*dibenzylhydroxylamine* (**1**). The title compound, m.p. 94–96°, was prepared as described[3] for the synthesis of the ^{18}O-labelled compound, m.p. 94–95°, except that equimolecular quantities of benzoyl peroxide and dibenzylamine were used. The IR ν_{max} 1720 (C=O) cm^{-1}; NMR ($CDCl_3$): δ 4·18 (s, 4H, CH_2), 6·90–7·95 (m, 15H, aromatic protons).

N-*Benzyl*-α-*phenylnitrone* (**7**). A soln of dibenzylamine (1·97 g) in dry acetone (10 ml) was cooled in ice and to it was added dropwise an ice-cold soln of *m*-chloroperbenzoic acid (3·80 g) in dry acetone (15 ml). The soln was maintained at *ca* 5° for 2 hr, then heated under reflux for a further 2 hr during which time a yellow colour developed. Evaporation gave a yellow solid which was partitioned between 10% K_2CO_3 (25 ml) and ether (50 ml). The yellow ether layer was washed (H_2O), dried (Na_2SO_4) and evaporated to give a pale yellow solid (1·79 g) which was recrystallized from aqueous EtOH to give the title compound as a colourless solid, m.p. 83–84°. Lit[14] m.p. 82–83°. MS: 211 (7) [M^+]; 91 (100) [$C_6H_5CH_2^+$] *m/e* (% rel.abund.); NMR ($CDCl_3$): δ 4·98 (s, 2H, CH_2), 7·15–7·55 (s, broad base, 9H, 8 aromatic protons and overlapping methine CH), 8·00–8·30 (m, 2H, ortho-protons on α-phenyl).

N,N-*Dibenzylhydroxylamine* (**2**). (a) A solution of O-benzoyl-N,N-dibenzylhydroxylamine (1·0 g) in dry ether (30 ml) was added dropwise and with stirring to a cooled suspension of LAH (0·2 g) in dry ether (20 ml). The mixture was then stirred for 1 hr at room temp and water was added dropwise to the cooled soln to decompose the complex and excess reagent. The ether layer was removed and the remaining white solid extracted with more ether (2 × 25 ml). The combined ether extract was evaporated to dryness. The colourless residue was suspended in cold light petroleum (b.p. 40–60°, 20 ml) and filtered to give the title compound (0·59 g), m.p. 125·5–127° (from aqueous acetone). Lit[3] m.p 125–126°, IR ν_{max} 3200 (OH) cm^{-1}. The compound readily reduced Tollen's reagent and had T_R = 8·0 min on the Carbowax column (oven temp 198°; carrier gas pressure 40 lb/sq in).

(b) A soln of N-benzyl-α-phenylnitrone (100 mg) in dry ether (10 ml) was reduced with LAH (85 mg) as described. Evaporation of the combined ether extract and trituration of the residue with light petroleum (40–60°) gave the title compound (74 mg), m.p. 124–126°, identical in behaviour to the product prepared by method (*a*).

N-*Hydroxy*-N-*methylamphetamine* (**9a**). A soln of *m*-chloroperbenzoic acid (3·85 g) in dry acetone (30 ml),

cooled in ice, was added dropwise over a 20 min period to an ice-cold soln of methylamphetamine (1·60 g) in the same solvent (15 ml). The mixture was left in an ice-bath for a further 30 min, then for 30 min at room temp. Evaporation *in vacuo* gave a colourless solid which was suspended in 10% K_2CO_3 (40 ml) and extracted with ether (3 × 50 ml). The combined ether soln was washed (H_2O) (10 ml), dried (Na_2SO_4) and evaporated to give an oil, ν_{max} 1720 cm^{-1} (ester C=O).

A soln of the oil in dry ether (40 ml) was added dropwise to a suspension of LAH (0·5 g) in dry ether (20 ml) at such a rate that gentle reflux was maintained (20 min) and refluxing was continued for a further 30 min. Excess water was added dropwise to the cooled soln and the ether layer was separated. The ppt was extracted with more ether (2 × 20 ml). The ether solns were combined, dried (Na_2SO_4) and evaporated to an oil which now lacked IR ester absorption. This oil was dissolved in dry ether (10 ml) and an excess of a soln of $(COOH)_2$ in dry ether was added in small portions until no more ppt formed, yield 1·89 g. A portion (5 mg) was suspended in 10% NaOH (0·2 ml) and extracted with ether (0·5 ml). The ether extract (5 μl) was GLC-examined on the 7½% carbowax column (oven temp 127°; carrier gas pressure 25 lbs/sq in) and it gave two peaks, (a) T_R 2·0 min (22% based on peak area; (b) T_R 24·2 min (78%). The former had a T_R value identical with that of N-methylamphetamine.

The oxalate (1·20 g) was suspended in pH 5·5 buffer soln (20 ml) and extracted with ether (5 × 50 ml). The combined ether extract was dried (Na_2SO_4) and evaporated to an oil. This was dissolved in dry ether (50 ml) and an excess of $(COOH)_2$ in dry ether was added. The resulting solid was crystallised from EtOH/ether to give **9a** acid oxalate (0·25 g), m.p. 147–149°, NMR (DMSO-d_6) δ 1·04 (d, 3H, J = 7, C—CH_3); 2·82 (s, 3H, $\overset{+}{N}$—CH_3) overlapping 2·30–3·60 (m, 3H, CH_2 and CH); 7·22 (s, 5H, aromatic protons); 10·70 (broad s, 3H, exchanges with D_2O, NHOH and COOH). MS:M^+ ion absent; 91 (33%) [$PhCH_2^+$]; 74 (66%) [$CH_3CH{=}\overset{+}{N}(OH)CH_3$]; 72 (77%) [$C_3H_6NO^+$]; 58 (100%) [$CH_3CH{=}\overset{+}{N}HCH_3$].

When the base (**9a**) was extracted into ether from a pH 13 soln of the oxalate and the ether soln GLC'd as described above, it gave a single peak, T_R 24·2 min. When the same ether solution was spotted on filter paper and sprayed with Tollen's reagent, a black colour developed instantly. Analytical data for **9a** is included in Table 1.

Additional N-*alkyl*-N-*hydroxyamphetamines* (**9b–9h**). These compounds were prepared in essentially the manner described for **9a** except that the optimal pH of the buffer soln used in the separation of **9** from **8** varied (Table 1). Generally, five 50 ml ether extracts of the buffered soln (50 ml) were made though it was established that this resulted in only 20–30% extraction of the N-hydroxy compound. In some instances, the initial precipitation of all basic products as oxalates from the ether soln remaining after the LAH reduction step was omitted. When this was so, the ether soln (100 ml) was extracted with aqueous buffer (100 ml). The aqueous layer was further extracted with ether (5 × 50 ml) and all ether solns combined.

Oxalates of the extracted compounds (**9b–9h**) were prepared as described for **9a** oxalate. Sometimes the addition of the ether soln of $(COOH)_2$ caused an immediate ppt of the salt as the acid oxalate. In other cases, the salt precipitated slowly on standing. These products were full oxalates. Repeated attempts to obtain **9c** oxalate in anhydrous form were unsuccessful.

General method for nitrone formation. To a soln of the oxalate (**9**, 10 mg) in distilled water, excess powdered yellow HgO (10 mg) was added and the suspension shaken for 10 min at room temp. The filtrate was extracted with ether (20 ml) and the ether extract concentrated (50 μl), then examined by GLC and combined GLC/MS.

General method for $TiCl_3$ *reduction of hydroxylamines.* To a soln of the hydroxylamine oxalate (**9**), (10 mg) in water (5 ml) was added 0·2 ml $TiCl_3$ soln (30% w/v in 24% w/v HCl). The mixture was kept in the dark for 20 min then basified (0·5 ml 5N NaOH) and extracted with ether (3 × 3 ml). The combined ether extract was concentrated (50 μl) and examined by GLC. T_R-values of products were compared with those of authentic reference compounds on the 7½% Carbowax column.

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